Medical Science

To Cite:
Chwiejczak J, Kościan J, Młynarska J, Górny A, Szczerkowska K, Wójcik A, Langa J, Obrębski M, Seroka A, Rybicka M. Air quality and aging brain: Air pollution as a risk factor of developing dementia. *Medical Science* 2024; 28: e49ms3349
doi: https://doi.org/10.54905/dissi.v28i147.e49ms3349

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Peer-Review History
Received: 18 March 2024
Reviewed & Revised: 22/March/2024 to 23/May/2024
Accepted: 27 May 2024
Published: 31 May 2024

Peer-review Method
External peer-review was done through double-blind method.

Medical Science
pISSN 2321–7359; eISSN 2321–7367

DISCOVERY SCIENTIFIC SOCIETY

Air quality and aging brain: Air pollution as a risk factor of developing dementia

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ABSTRACT

Introduction and Purpose: Air pollution is one of the underrated risk factors for developing major health problems in the contemporary world, such as cardiovascular and respiratory diseases, stroke, and lung cancer. Almost 99% of the global population resides in areas where air quality standards set by the World Health Organization (WHO) are exceeded. This review article aims to explore the latest data regarding the link between air pollution and dementia, as well as the main challenges in research in this field. These findings are crucial for implementing proper prevention strategies for neurodegenerative diseases and reducing the prevalence of dementia. *Brief description of the state of knowledge*: Recent studies suggest that air pollution could influence the brain and contribute to the development of dementia. The compounds primarily suspected negatively impacting health include particulate matter (PM10 and PM2.5), ozone (O3), nitrogen dioxide (NO2), carbon monoxide (CO), and sulfur dioxide (SO2). The strongest correlation between exposure to air pollutants and increased risk of developing dementia was found for PM2.5 in numerous studies. *Summary:* The strongest association was found for PM2.5, while PM10, NO2, and NOx are potentially harmful. Most studies have been conducted in high-income countries, highlighting the need for data from middle and low-income countries. There is insufficient research regarding O3, SO2, and CO. Given that air pollution is ubiquitous in the modern world and affects most of the world's population, further research in this field is necessary.

Keywords: Dementia, air pollution, ambient pollution, Alzheimer's disease, particulate matter

1. INTRODUCTION

Dementia is a term used to describe a group of diseases that cause the loss of brain function, particularly affecting short and long-term memory, which leads to difficulties in daily functioning, information retrieval, and cognitive processes. Currently, 55 million people worldwide have dementia, with 60% of them residing in low and middle-income countries. However, 74% of the costs occur in high income countries (Wimo et al., 2023). According to the WHO, the number of patients who have dementia is projected to triple by 2050. The estimated global economic cost of dementia is 1.3 trillion dollars and it has risen by 60% between 2010 and 2019, and is expected to double by 2030. Informal care accounts for 50% of the costs.

There are several types of dementia, including Alzheimer's disease, dementia with Lewy bodies, frontotemporal dementia, vascular dementia, Parkinson's disease dementia, and posterior cortical atrophy. There are several identified risk factors for developing dementia, including smoking, being overweight, diabetes, hypertension, alcoholism, social isolation, depression, and age over 65 years. One of the latest discovered risk factors is air pollution. The first article suggesting a connection between air pollution and potential central nervous system damage leading to dementia was published in 2004 (Calderón-Garcidueñas et al., 2004). The study revealed a strong correlation between dogs exposed to air pollution and an acceleration of Alzheimer-like pathology in their brains (Calderón-Garcidueñas et al., 2004). These surprising results prompted further investigation into the impact of air pollution on the human central nervous system.

Air pollution is a significant problem that affects people regardless of the country they live in. According to the WHO, 99% of the world's population lives in areas where the thresholds for key air pollutants are greatly exceeded. In 2019, WHO research reported that 4.2 million premature deaths were caused by air pollution. Ambient pollution typically consists of PM, metals (such as nickel and lead), gases (including O3, NO2, NOx, and SO2), and organic compounds (such as benzene). PM is one of the most common air pollutants (United States Environmental Protection Agency, 2023). The primary sources of anthropogenic ambient air pollution include the incomplete combustion of fuels, which vehicles (such as cars, motorcycles, buses, trucks, and other forms of transportation) produce; industrial emissions from power plants, factories, and refineries; agricultural activities such as fertilization, pesticides, and herbicides; and poor waste management, including the burning of waste materials.

There are multiple possible pathomechanisms of neurodegeneration due to ambient pollution, including neuroinflammation, direct neurotoxicity, and oxidative stress (White et al., 2020; Hahad et al., 2021). The size of particulate matter corresponds to its different compositions and, therefore, varied effects on the human body (Thangavel et al., 2022; Valavanidis et al., 2008; Costa et al., 2020). The smaller the diameter of a pollutant particle, the easier it can penetrate the human body, increasing the risk of causing harm to the brain (Valavanidis et al., 2008). PM10 refers to particles approximately 10 micrometers in diameter, which can reach the upper respiratory tract (Block and Calderón-Garcidueñas, 2009). PM2.5, on the other hand, represents particles of approximately 2.5 micrometers in diameter, capable of reaching the lower respiratory tract (Block and Calderón-Garcidueñas, 2009). Particles smaller than 1 micrometer can reach the alveoli, while ultrafine particles, less than 0.1 micrometers in size, can directly access the bloodstream and break the blood-brain barrier (Block and Calderón-Garcidueñas, 2009; Oberdörster et al., 2004).

Particles that reach the brain directly may impact microglia and trigger neuroinflammation, leading to central nervous system damage (Costa et al., 2020). Those in the lungs can trigger inflammation, leading to the production of cytokines such as tumor necrosis factor-alpha (TNF-Alpha) and interleukin-1β (IL-1 β), which can disrupt the blood-brain barrier, upregulate cyclooxygenase-2 (COX-2), and activate nuclear factor kappa-light-chain-enhancer of activated B cells (NFkappaB) (Hahad et al., 2021). These reactions induce chronic oxidative stress and deoxyribonucleic acid (DNA) damage (Calderón-Garcidueñas et al., 2004). Moreover, exposure to air pollution may trigger the accumulation of amyloid beta 42 and alpha-synuclein, leading to a higher risk of developing neurodegenerative diseases such as Alzheimer's disease (Calderón-Garcidueñas et al., 2008).

In addition to mechanical inhalation into the lungs, ambient pollution can trigger damage and inflammation through direct translocation via the olfactory nerve (Hahad et al., 2021; Costa et al., 2017; Costa et al., 2020). It is noteworthy that olfactory deficit is one of the early signs of Alzheimer's disease (Liu et al., 2024; Fatuzzo et al., 2023). Some articles suggest it could be the leadning portal of entry for pollutants (Doty, 2008). Air pollution exposition may also activate the hormonal stress axis and influence the brain through the vagus nerve (Kodavanti, 2016). All of the processes mentioned above occur throughout a lifespan, starting from the early years and

leading to the accumulation of amyloid beta 42 and alpha-synuclein (Calderón-Garcidueñas et al., 2004). These processes should be considered as possible causes of Alzheimer's disease developed later in life.

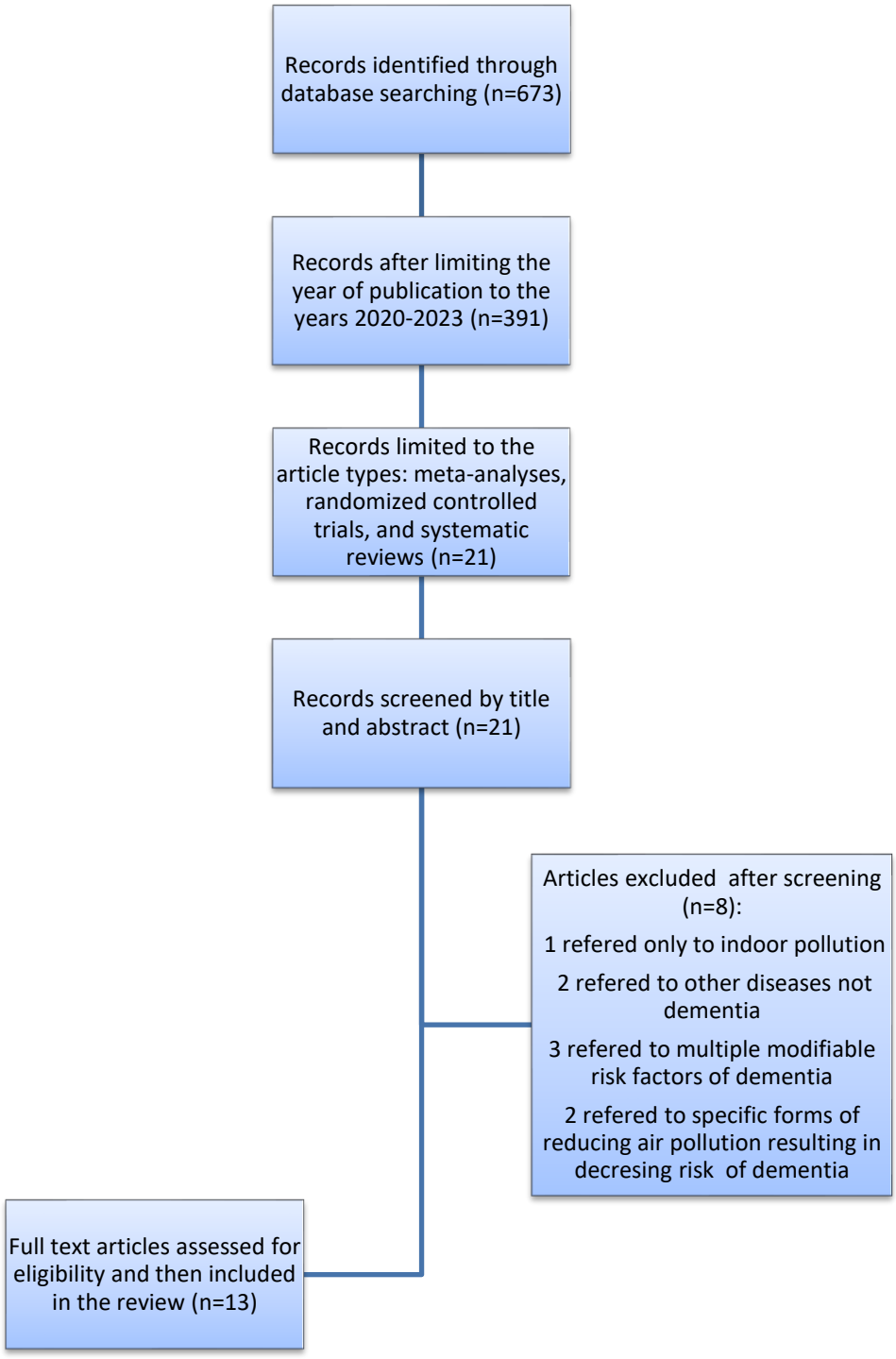

Figure 1 Summary of the research and the processing of information

Aim

The study aims to summarize the latest research regarding the correlation between air pollution exposure and the risk of developing dementia and cognitive decline in the adult population. Additionally, it aims to raise awareness of the air pollution problem and its impact on the brain.

2. METHODS

The search used medical databases such as PubMed and Web of Science. The following keywords were used to find relevant articles: ("Alzheimer" OR "Dementia" OR "Neurodegeneration") AND ("air pollution" OR "ambient pollution" OR "particulate matter"). The types of articles included in the research were meta-analyses, randomized controlled trials, and systematic reviews. The publication range was limited to the years 2020 to 2023. Initially, 21 articles were found that met the criteria. After further analysis based on relevance and quality, 13 articles were chosen for inclusion. Articles regarding only indoor air pollution or papers not focusing particularly on dementia or Alzheimer's disease in the context of ambient pollution were excluded. Figure 1 provides the summary of the research and the processing of information.

3. REVIEW

The prevalence of dementia worldwide is on the rise, emphasizing the urgent need to identify risk factors and mitigate their impact on patients' lives (Nichols and Vos, 2021). Table 1 shows the summary of the studies analyzed in this review. Recent scientific studies indicate a strong correlation between PM2.5 exposure and an increased risk of developing dementia. A Chinese meta-analysis Fu and Yung, (2020) suggests a significant association between PM2.5 pollution and Alzheimer's Disease incidence, with an odds ratio (OR) of 1.95 (95% CI: 0.88-4.30) per 10μg/m3 increase in PM2.5 concentration. The OR for other compounds were 1.03 (95% CI: 0.68-1.57) for O3, 1.00 (95% CI: 0.89-1.13) for NO2, and 0.95 (95% CI: 0.91-0.99) for PM10 (based on only one study). Furthermore, the OR was higher in more polluted areas (OR 2.20 vs OR 1.06 for lightly polluted areas). While research on CO and SO2 is limited, current knowledge suggests they may also increase the risk of developing Alzheimer's disease.

Another study by Peters et al., (2021) suggests a strong correlation between high concentrations of PM2.5 and dementia. It emphasizes that PM2.5 could directly and independently lead to Alzheimer's disease despite adjustments for the presence of cardiovascular comorbidities in most studies. In a meta-analysis conducted by Balboni et al., (2022), a strong inverse correlation was found between high concentrations of PM2.5 and the volume of the hippocampus measured by magnetic resonance imaging. However, the correlation regarding PM10 was weaker, and no association was found regarding NO2. These findings highlight how air pollution may contribute to memory loss, cognitive decline, and ultimately, dementia. An American systematic review Weuve et al., (2021), based on 35 included studies, reported that PM2.5 findings generally support a correlation between dementia and PM2.5 pollution.

However, it suggests there are insufficient papers concerning ozone to draw any conclusions, and the findings regarding PM10, NO2, and NOx are inconclusive. In a Chinese meta-analysis Zhao et al., (2021), scientists analyzed 22 environmental factors possibly contributing to the development of dementia. With high-to-moderate quality evidence, the risk of exposure to the following factors was researched: PM2.5 (HR=1.24, 95% CI: 1.17-1.31), NO2 (HR=1.07, 95% CI: 1.02-1.12), aluminum (OR=1.35, 95% CI: 1.14-1.59), and solvents (OR=1.14, 95% CI: 1.07-1.22). Interestingly, no associations were observed regarding NOx and PM10. The data regarding SO2 was of low quality, but it may still be considered a possible risk factor. An Italian systematic review Cristaldi et al., (2021) examined the possible mechanisms of influence of PM2.5 on the brain, highlighting its potential connection with dementia. The research found that this connection not only depends on the patient's age, level of PM2.5 concentration, and duration of exposure but also on exposure to other air pollutants, comorbidities, and proximity to areas with high vehicular traffic.

PM2.5 promotes neuroinflammation, with particles being transferred to the brain through the nasal epithelium and olfactory bulb. Additionally, PM2.5 triggers the expression of markers of neurodegenerative diseases, such as alpha-synuclein or beta-amyloid, potentially leading to the development of neurodegenerative diseases. Despite these findings, the exact molecular and cellular mechanisms of PM2.5 exposure leading to neurodegenerative diseases remain unknown and require further research. An Indian review article Chandra et al., (2022) suggests that exposure to high levels of PM2.5, polycyclic aromatic hydrocarbons (PAHs), NO2, and persistent organic pollutants (POPs) correlates with cognitive decline, neurodegeneration, and the development of dementia. The

article notes a lack of sufficient data from low-income countries, with most research coming from Europe and the USA. The results from high-income countries may not apply to low-income countries due to differences in the composition of air pollution.

Moreover, in low-income countries, the composition of indoor air pollution, such as using wood stoves for cooking indoors, differs. The research also highlights that PM2.5 could trigger neuroinflammation and the expression of pro-inflammatory mediators like TNF-α, IL-1β, and reactive oxygen species (ROS). Another investigation conducted by Dhiman et al., (2022) posits that exposure to PM2.5 may serve as a risk factor for the development of dementia. While ozone is a potential risk factor, the findings regarding NOx and NO2 differed from those of previously mentioned studies. In terms of all-cause dementia, the pooled hazard ratio (HR) for PM2.5 and NO2 exposure was 1.03 ((95% CI: 1.01-1.06; I2 = 99% (P < 0.001)) and 1.00 ((95% CI: 1.00-1.01; I2 = 96% (P < 0.001)), respectively. Specifically for Alzheimer's disease, the HR was 1.08 (95% CI: 1.01-1.15; I2 = 99% (P < 0.001)) for PM2.5 and 1.02 (95% CI: 0.96-1.08; I2 = 100% (P < 0.001)) for O3.

Unfortunately, there were no eligible studies available to conduct a meta-analysis for SO2 and CO. The authors of the study caution against generalizing the results to low-income countries and emphasize the need for further research. A Chinese meta-analysis by Cheng et al., (2022) concluded that exposure to high concentrations of PM2.5 could result in developing dementia. The following HRs were obtained: 1.40 (95% CI 1.23, 1.60) for dementia, 1.47 (95% CI 1.22, 1.78) for Alzheimer's Disease, and 2.00 (95% CI 1.30, 3.08) for vascular dementia per 10.0 μg/m3 PM2.5 increase. A meta-analysis conducted by Abolhasani et al., (2022) examined the correlation between PM2.5 and the incidence of dementia. The research shows that a 1 μg/m3 increment in PM2.5 leads to an increase in the risk of developing dementia by 3% (HR, 1.03; 95% CI (1.02 -1.05); I2 = 100%). Increment per 10 μg/m3 in NOx (HR, 1.05; 95% CI (0.99-1.13); I2 = 61%), NO2 (HR, 1.03; 95% CI (1.00-1.07); I2 = 94%), and O3 levels (HR, 1.01; 95% CI (0.91-1.11); I2 = 82%) was not clearly correlated with developing dementia, but these compounds require further research.

A Chinese meta-analysis by Tang et al., (2023) demonstrated an approximately 13% increase in the risk of developing dementia concerning overall air pollution exposure. The following compounds were associated with an increased risk: PM2.5, PM10, CO, NO2, and NOx. However, O3 exposure did not increase the risk of dementia. Another meta-analysis by Gong et al., (2023) focused on the correlation between long-term exposure to PM2.5 and neurodegenerative diseases. A significant positive correlation was found, with a pooled OR of 1.30 for all-cause dementia (95% CI: 1.14, 1.47, I2 = 99.3%) and 1.65 for Alzheimer's disease (95% CI: 1.37, 1.94, I2 = 98.2%). The researchers also found a positive correlation between long-term PM2.5 exposure and cognitive decline.

An American meta-analysis Wilker et al., (2023) suggests a strong association between PM2.5 exposure and the risk of developing dementia. The HR per 2 μg/m3 PM2.5 was 1.04 (95% confidence interval 0.99 to 1.09). Furthermore, this correlation exists even in cases of exposure to PM2.5 concentrations below the current limits in the European Union (25 μg/m3), the United Kingdom (25 μg/m3), and the current United States Environmental Protection Agency standards (12 μg/m3). The detrimental effects of NO2 and NOx were also observed, although the data was limited. The overall HR per 10 μg/m3 NO2 was 1.02 (0.98 to 1.06), and per 10 μg/m3 NO was 1.05 (0.98 to 1.13). The HR per 5 μg/m3 O3 was 1.00 (0.98 to 1.05), suggesting no clear association with the risk of developing dementia.

Table 1 Studies on the association between air pollution and different air pollutants

Study	Year	The air pollutants	Results
Fu and Yung	2020	PM2.5, O3, NO2, PM10, SO2, CO	PM2.5 – the strongest association with increased risk of dementia O3, NO2, PM10, SO2, CO – may potentially increase the risk dementia
Peters et al.,	2021	PM2.5	PM2.5 – strong association with increased risk of dementia

Balboni et al.,	2022	PM2.5, PM10, NO2	PM2.5 – strong association with low hippocampal volume PM10 – weak association with low hippocampal volume NO2 – no association
Weuve et al.,	2021	PM2.5, PM10, NO2, NOx, O3	PM2.5- adverse association with cognitive decline PM10, NO2, NOx O3 – not enough data to draw conclusions
Zhao et al.,	2021	PM2.5, PM10, NO2, solvents, aluminium, SO2, NOx	PM2.5, NO2, aluminium, solvents – strong association with increased risk of dementia PM10, NOx – no association found with increased risk of dementia SO2 – not enough data to draw conclusions
Cristaldi et al.,	2021	PM2.5	PM2.5 - strong association with increased risk of dementia
Chandra et al.,	2022	Polycyclic aromatic hydrocarbons (PAH), NO2, PM, persistent organic pollutants (POPs)	PAH, NO2, PM, POPs – strong association with cognitive decline
Dhiman et al.,	2022	PM2.5, O3 NO2/NOx, PM10, CO, SO2	PM2.5 - strong association with increased risk of dementia O3 - weak association with increased risk of AD NO2/NOx, PM10, CO, SO2 – not enough data to draw clear conclusions
Cheng et al.,	2022	PM2.5	PM2.5 - strong association with increased risk of dementia

Abolhasani et al.,	2022	PM2.5, NOX, NO2, O3	PM2.5 - strong association with increased risk of dementia NOx, NO2, O3 - not clearly correlated with developing dementia
Tang et al.,	2023	PM2.5, PM10, NOX, NO2, O3, CO	PM2.5, PM10, NOX, NO2, - strong association with increased risk of dementia O3 - not correlated with developing dementia
Gong et al.,	2023	PM2.5, PM10	PM2.5, PM10 - strong association with increased risk of dementia
Wilker et al.,	2023	PM2.5, NO, NO2, O3	PM2.5 - strong association with increased risk of dementia NO, NO2 - moderate association with increased risk of dementia due to limited data O3 - not correlated with developing dementia

4. DISCUSSION

Based on the reviewed literature (Table 1), PM2.5 is identified as the primary component of air pollution associated with an increased risk of developing dementia. Research on the correlation between ambient air pollution and dementia predominantly focuses on PM2.5, with only a few studies analyzing O3. Among these studies, only two Fu and Yung, (2020), Dhiman et al., (2022) identified O3 as a possible risk factor for neurodegeneration. The remaining publications suggest either insufficient or low-quality data regarding O3, making it challenging to draw clear conclusions. There is also no consensus among scientists regarding the association of NO, NO2, PM10, CO, and SO2 with dementia development. While these compounds could potentially be associated with dementia, the available data cannot confirm or refute their role. Further research in this area is therefore essential.

Several studies underscore the limitations inherent in current research and data analysis methodologies. There is an urgent need for standardized data collection practices. For example, many studies lack detailed compositional information about fine particles despite variations in composition across countries and over time. Furthermore, there is limited research coverage on O3, NO2, CO, and SO2. Middle and low-income countries are particularly underrepresented in research efforts, despite experiencing significant exceedances of air quality standards in these regions. This disparity may be attributed to the reliance of lower-income countries on heavy industry and high-polluting technologies (Rentschler and Leonova, 2023). Consequently, data from middle and low-income countries are crucial for future research.

5. CONCLUSIONS

Air pollution can indeed be considered a risk factor for developing dementia, but additional research is needed to understand its impact. Among air pollutants, PM2.5 has received the most extensive research attention and is supported by robust scientific evidence. However, other particles such as NO, NO2, PM10, CO, SO2, and PM10 require further high-quality research to elucidate their potential association with dementia. Importantly, there is an urgent need for data from middle and low-income countries, where air quality standards are often exceeded, and research on this topic is limited. Current research suggests that public health officials, healthcare professionals, and policymakers should take steps to reduce population exposure to air pollutants to mitigate the prevalence of dementia and its adverse societal impacts. This highlights the importance of proactive measures to address air pollution as a public health concern.

Author's Contributions

Justyna Chwiejczak, Jan Kościan, Julita Młynarska: Conceptualization
Aleksander Górny, Jan Kościan: Methodology
Julita Młynarska, Karolina Szczerkowska: Formal analysis
Karolina Szczerkowska, Aleksander Górny: Resources, data curation
Anna Seroka, Maria Rybicka, Justyna Chwiejczak, Aleksander Górny: Investigation
Michał Obrębski, Jakub Langa, Justyna Chwiejczak: Writing, rough preparation
Anna Wójcik, Anna Seroka, Maria Rybicka: Writing, review and editing
Karolina Szczerkowska: Visualization

Funding

This study has not received any external funding.

Ethical approval

Not applicable.

Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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